MAR 28 2000

NDA 16-949/S-027/S-031/S-032

Hoffmann-LaRoche Inc.
Attention: Anthony Corrado
Drug Regulatory Affairs
340 Kingsland Street
Nutley, NJ 07110-1199

Dear Mr. Corrado:

Please refer to your supplemental new drug applications dated March 1, 1988 (S-027), October 3, 1995 (S-031), and February 2, 1996 (S-032), submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Limbitrol (chlordiazepoxide and amitriptyline hydrochloride) Tablets.

We acknowledge receipt of your amendments submitted to S-032 dated April 4, 1996, and July 11, 1996.

These supplemental new drug applications provide for the following revisions to product labeling:

16-949/S-027

1. The addition of a new section entitled **DRUG ABUSE AND DEPENDENCE** to replace the **Physical and Psychological Dependence** subsection under **WARNINGS.**

2. The addition of a sentence under **WARNINGS** to refer the reader to the **DRUG ABUSE AND DEPENDENCE** section

3. The addition of a new subsection under the **PRECAUTIONS** section entitled **Information for Patients.**

We note that these revisions were requested in Agency letters dated July 6, 1987, and January 5, 1988.

16-949/S-031

1. The addition of a new subsection under the **PRECAUTIONS** section entitled **Drugs Metabolized by P4502D6**. This revision was requested in an Agency letter dated June 15, 1994.

2. The revision of the **DESCRIPTION** section to reflect a fonnulation change for use of an engraved aqueous film-coated tablets and revised inactive ingredient and color listings.

16-949/S-032

1. This supplement provides for a complete revision of the **OVERDOSE** section as requested in an Agency letter dated October 3, 1995. This supplement was subsequently amended in a submission

dated July 11, 1996, as requested in an Agency letter dated March 8, 1996, to provide for a **Chlordiazepoxide Overdosage** subsection.

We have completed the review of these supplemental applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the submitted final printed labeling (package insert submitted July 11, 1996 (Label Code 26334520-0696), which incorporates all of the revisions listed above. Accordingly, these supplemental applications are approved effective on the date of this letter.

Labeling changes of the kind which you have proposed are permitted by section 314.70(c) of the regulations to be instituted prior to approval of the supplement. It is understood that the changes, described in the above NDA supplements, have been made.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Paul David, R.Ph., Regulatory Management Officer, at (301) 594-5530.

Sincerely,

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

LIMBITROL®

(chlordiazepoxide and amitriptyline HCl)

DS (double strength) TABLETS
TABLETS

Tranquilizer—Antidepressant

DESCRIPTION: Limbitrol combines for oral administration, chlordiazepoxide, an agent for the relief of anxiety and tension, and amitriptyline, an antidepressant. It is available in DS (double strength) white, film-coated tablets, each containing 10 mg chlordiazepoxide and 25 mg amitriptyline (as the hydrochloride salt); and in blue, film-coated tablets, each containing 5 mg chlordiazepoxide and 12.5 mg amitriptyline (as the hydrochloride salt). Each tablet also contains corn starch, hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose, magnesium stearate, polyethylene glycol, povidone and propylene glycol; Limbitrol tablets contain the following colorant system--FD&C Blue No. 1 aluminum lake and titanium dioxide; Limbitrol DS tablets contain titanium dioxide.

Chlordiazepoxide is a benzodiazepine with the formula 7-chloro-2-(methylamino)-5-phenyl-3 *H* -1,4-benzodiazepine 4-oxide. It is a slightly yellow crystalline material and is insoluble in water. The molecular weight is 299.76.

Amitriptyline is a dibenzocycloheptadiene derivative. The formula is 10,11-dihydro-N,N-dimethyl-5H-dibenzo [a,d] cycloheptene-$\Delta^{5,}{}_{m}$-propylamine hydrochloride. It is a white or practically white crystalline compound that is freely soluble in water. The molecular weight is 313.87.

ACTIONS: Both components of Limbitrol exert their action in the central nervous system. Extensive studies with chlordiazepoxide in many animal species suggest action in the limbic system. Recent evidence indicates that the limbic system is involved in emotional response. Taming action was observed

in some species. The mechanism of action of amitriptyline in man is not known, but the drug appears to interfere with the reuptake of norepinephrine into adrenergic nerve endings. This action may prolong the sympathetic activity of biogenic amines.

INDICATIONS: Limbitrol is indicated for the treatment of patients with moderate to severe depression associated with moderate to severe anxiety.

The therapeutic response to Limbitrol occurs earlier and with fewer treatment failures than when either amitriptyline or chlordiazepoxide is used alone.

Symptoms likely to respond in the first week of treatment include: insomnia, feelings of guilt or worthlessness, agitation, psychic and somatic anxiety, suicidal ideation and anorexia.

CONTRAINDICATIONS: Limbitrol is contraindicated in patients with hypersensitivity to either benzodiazepines or tricyclic antidepressants. It should not be given concomitantly with a monoamine oxidase inhibitor. Hyperpyretic crises, severe convulsions and deaths have occurred in patients receiving a tricyclic antidepressant and a monoamine oxidase inhibitor simultaneously. When it is desired to replace a monoamine oxidase inhibitor with Limbitrol, a minimum of 14 days should be allowed to elapse after the former is discontinued. Limbitrol should then be initiated cautiously with gradual increase in dosage until optimum response is achieved.

This drug is contraindicated during the acute recovery phase following myocardial infarction.

WARNINGS: Because of the atropine-like action of the amitriptyline component, great care should be used in treating patients with a history of urinary retention or angle-closure glaucoma. In patients with glaucoma, even average doses may precipitate an attack. Severe constipation may occur in patients taking tricyclic antidepressants in combination with anticholinergic-type drugs.

Patients with cardiovascular disorders should be watched closely. Tricyclic antidepressant drugs, particularly when given in high doses, have been reported to produce arrhythmias, sinus tachycardia and prolongation of conduction time. Myocardial infarction and stroke have been reported in patients receiving drugs of this class.

Because of the sedative effects of Limbitrol, patients should be cautioned about combined effects with alcohol or other CNS depressants. The additive effects may produce a harmful level of sedation and CNS depression.

Patients receiving Limbitrol should be cautioned against engaging in hazardous occupations requiring complete mental alertness, such as operating machinery or driving a motor vehicle.

Usage in Pregnancy: Safe use of Limbitrol during pregnancy and lactation has not been established. Because of the chlordiazepoxide component, please note the following:

> **An increased risk of congenital malformations associated with the use of minor tranquilizers (chlordiazepoxide, diazepam and meprobamate) during the first trimester of pregnancy has been suggested in several studies. Because use of these drugs is rarely a matter of urgency, their use during this period should almost always be avoided. The possibility that a woman of childbearing potential may be pregnant at the time of institution of therapy should be considered. Patients should be advised that if they become pregnant during therapy or intend to become pregnant they should communicate with their physicians about the desirability of discontinuing the drug.**

Withdrawal symptoms of the barbiturate type have occurred after the discontinuation of benzodiazepines. (See DRUG ABUSE AND DEPENDENCE section.)

PRECAUTIONS: *General:* Use with caution in patients with a history of seizures.

Close supervision is required when Limbitrol is given to hyperthyroid patients or those on thyroid medication.

The usual precautions should be observed when treating patients with impaired renal or hepatic function.

Patients with suicidal ideation should not have easy access to large quantities of the drug. The possibility of suicide in depressed patients remains until significant remission occurs.

Essential Laboratory Tests: Patients on prolonged treatment should have periodic liver function tests and blood counts.

Drug and Treatment Interactions: Because of its amitriptyline component, Limbitrol may block the antihypertensive action of guanethidine or compounds with a similar mechanism of action.

Drugs Metabolized by P450 2D6: The biochemical activity of the drug metabolizing isozyme cytochrome P450 2D6 (debrisoquin hydroxylase) is reduced in a subset of the caucasian population (about 7% to 10% of caucasians are so called "poor metabolizers"); reliable estimates of the prevalence of reduced P450 2D6 isozyme activity among Asian, African and other populations are not yet available. Poor metabolizers have higher than expected plasma concentrations of tricyclic antidepressants (TCAs) when given usual doses. Depending on the fraction of drug metabolized by P450 2D6, the increase in plasma concentration may be small or quite large (8-fold increase in plasma AUC of the TCA).

In addition, certain drugs inhibit the activity of this isozyme and make normal metabolizers resemble poor metabolizers. An individual who is stable on a given dose of TCA may become abruptly toxic when given one of these inhibiting drugs as concomitant therapy. The drugs that inhibit cytochrome P450 2D6 include some that are not metabolized by the enzyme (quinidine; cimetidine) and many that are substrates for P450 2D6 (many other antidepressants, phenothiazines, and the type 1c antiarrhythmics propafenone and flecainide). While all the selective serotonin reuptake inhibitors (SSRIs), eg, fluoxetine, sertraline and paroxetine, inhibit P450 2D6, they may vary in the extent of inhibition. The extent to which SSRI TCA interactions may pose clinical problems will depend on the degree of inhibition and the pharmacokinetics of the SSRI involved. Nevertheless, caution is indicated in the coadministration of TCAs with any of the SSRIs and also in switching from one class to the other. Of particular importance, sufficient time must elapse before initiating TCA treatment in a patient being withdrawn from fluoxetine, given the long half-life of the parent and active metabolite (at least 5 weeks may be necessary).

Concomitant use of tricyclic antidepressants with drugs that can inhibit cytochrome P450 2D6 may require lower doses than usually prescribed for either the tricyclic antidepressant or the other drug. Furthermore, whenever one of these other drugs is withdrawn from cotherapy, an increased dose of tricyclic antidepressant may be required. It is desirable to monitor TCA plasma levels whenever a TCA is going to be coadministered with another drug known to be an inhibitor of P450 2D6.

The effects of concomitant administration of Limbitrol and other psychotropic drugs have not been evaluated. Sedative effects may be additive.

Cimetidine is reported to reduce hepatic metabolism of certain tricyclic antidepressants and benzodiazepines, thereby delaying elimination and increasing steady-state concentrations of these drugs. Clinically significant effects have been reported with the tricyclic antidepressants when used concomitantly with cimetidine (Tagamet).

The drug should be discontinued several days before elective surgery.

Concurrent administration of ECT and Limbitrol should be limited to those patients for whom it is essential.

Pregnancy: See WARNINGS section.

Nursing Mothers: It is not known whether this drug is excreted in human milk. As a general rule, nursing should not be undertaken while a patient is on a drug, since many drugs are excreted in human milk.

Pediatric Use: Safety and effectiveness in children below the age of 12 years have not been established.

Elderly Patients: In elderly and debilitated patients it is recommended that dosage be limited to the smallest effective amount to preclude the development of ataxia, oversedation, confusion or anticholinergic effects.

Information for Patients: To assure the safe and effective use of benzodiazepines, patients should be informed that, since benzodiazepines may produce psychological and physical dependence, it is advisable that they consult with their physician before either increasing the dose or abruptly discontinuing this drug.

ADVERSE REACTIONS: Adverse reactions to Limbitrol are those associated with the use of either component alone. Most frequently reported were drowsiness, dry mouth, constipation, blurred vision, dizziness and bloating. Other side effects occurring less commonly included vivid dreams, impotence, tremor, confusion and nasal congestion. Many symptoms common to the depressive state, such as anorexia, fatigue, weakness, restlessness and lethargy, have been reported as side effects of treatment with both Limbitrol and amitriptyline.

Granulocytopenia, jaundice and hepatic dysfunction of uncertain etiology have also been observed rarely with Limbitrol. When treatment with Limbitrol is prolonged, periodic blood counts and liver function tests are advisable.

Note: Included in the listing which follows are adverse reactions which have not been reported with Limbitrol. However, they are included because they have been reported during therapy with one or both of the components or closely related drugs.

Cardiovascular: Hypotension, hypertension, tachycardia, palpitations, myocardial infarction, arrhythmias, heart block, stroke.

Psychiatric: Euphoria, apprehension, poor concentration, delusions, hallucinations, hypomania and increased or decreased libido.

Neurologic: Incoordination, ataxia, numbness, tingling and paresthesias of the extremities, extrapyramidal symptoms, syncope, changes in EEG patterns.

Anticholinergic: Disturbance of accommodation, paralytic ileus, urinary retention, dilatation of urinary tract.

Allergic: Skin rash, urticaria, photosensitization, edema of face and tongue, pruritus.

Hematologic: Bone marrow depression including agranulocytosis, eosinophilia, purpura, thrombocytopenia.

Gastrointestinal: Nausea, epigastric distress, vomiting, anorexia, stomatitis, peculiar taste, diarrhea, black tongue.

Endocrine: Testicular swelling and gynecomastia in the male, breast enlargement, galactorrhea and minor menstrual irregularities in the female, elevation and lowering of blood sugar levels, and syndrome of inappropriate ADH (antidiuretic hormone) secretion.

Other: Headache, weight gain or loss, increased perspiration, urinary frequency, mydriasis, jaundice, alopecia, parotid swelling.

DRUG ABUSE AND DEPENDENCE: Withdrawal symptoms, similar in character to those noted with barbiturates and alcohol (convulsions, tremor, abdominal and muscle cramps, vomiting and sweating), have occurred following abrupt discontinuance of chlordiazepoxide. The more severe withdrawal symptoms have usually been limited to those patients who had received excessive doses over an extended period of time. Generally milder withdrawal symptoms (eg, dysphoria and insomnia) have been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic levels for several months. Withdrawal symptoms (eg, nausea, headache and malaise) have also been reported in association with abrupt amitriptyline discontinuation. Consequently, after extended therapy, abrupt discontinuation should generally be avoided and a gradual dosage tapering schedule followed. Addiction-prone individuals (such as drug addicts or alcoholics) should be under careful surveillance when receiving chlordiazepoxide or other psychotropic agents because of the predisposition of such patients to habituation and dependence.

OVERDOSAGE*: Deaths may occur from overdosage with this class of drugs. Multiple drug ingestion (including alcohol) is common in deliberate tricyclic antidepressant overdose. As the management is complex and changing, it is recommended that the physician contact a poison control center for current information on treatment. Signs and symptoms of toxicity develop rapidly after tricyclic antidepressant overdose; therefore, hospital monitoring is required as soon as possible.

Manifestations: Critical manifestations of overdose include: cardiac dysrhythmias, severe hypotension, convulsions and CNS depression, including coma. Changes in the electrocardiogram, particularly in QRS axis or width, are clinically significant indicators of tricyclic antidepressant toxicity.

Other signs of overdose may include: confusion, disturbed concentration, transient visual hallucinations, dilated pupils, agitation, hyperactive reflexes, stupor, drowsiness, muscle rigidity, vomiting, hypothermia, hyperpyrexia or any of the symptoms listed under ADVERSE REACTIONS.

Management: *General:* Obtain an ECG and immediately initiate cardiac monitoring. Protect the patient's airway, establish an intravenous line and initiate gastric decontamination. A minimum of 6 hours of observation with cardiac monitoring and observation for signs of CNS or respiratory depression, hypotension, cardiac dysrhythmias and/or conduction blocks, and seizures is necessary. If signs of toxicity occur at any time during this period, extended monitoring is required. *There are case reports of patients succumbing to fatal dysrhythmias late after overdose; these patients had clinical evidence of significant poisoning prior to death and most received inadequate gastrointestinal decontamination.* Monitoring of plasma drug levels should not guide management of the patient.

Gastrointestinal Decontamination: All patients suspected of tricyclic antidepressant overdose should receive gastrointestinal decontamination. This should include large volume gastric lavage followed by activated charcoal. If consciousness is impaired, the airway should be secured prior to lavage. Emesis is contraindicated.

Cardiovascular: A maximal limb-lead QRS duration of $ 0.10 seconds may be the best indication of the severity of the overdose. Serum alkalinization, to a pH of 7.45 to 7.56, using intravenous sodium bicarbonate and hyperventilation (as needed) should be instituted for patients with dysrhythmias and/or QRS widening. A pH > 7.60 or a pCO_2 < 20 mm Hg is undesirable. Dysrhythmias unresponsive to sodium bicarbonate therapy/hyperventilation may respond to lidocaine, bretylium or phenytoin. Type *1A and 1C* antiarrhythmics are generally contraindicated (eg, quinidine, disopyramide and procainamide).

In rare instances, hemoperfusion may be beneficial in acute refractory cardiovascular instability in patients with acute toxicity. However, hemodialysis, peritoneal dialysis, exchange transfusions and forced diuresis generally have been reported as ineffective in tricyclic antidepressant poisoning.

CNS: In patients with CNS depression, early intubation is advised because of the potential for abrupt deterioration. Seizures should be controlled with benzodiazepines, or if these are ineffective, other anticonvulsants (eg, phenobarbital, phenytoin). *Physostigmine is not recommended except to treat life-threatening symptoms that have been unresponsive to other therapies,* and then only in consultation with a poison control center.

Psychiatric Follow-up: Since overdosage is often deliberate, patients may attempt suicide by other means during the recovery phase. Psychiatric referral may be appropriate.

Pediatric Management: The principles of management of child and adult overdosages are similar. It is strongly recommended that the physician contact the local poison control center for specific pediatric treatment.

*Poisindex® Toxicologic Management. Topic: Antidepressants, Tricyclic. *Micromedex Inc.* Vol. 85.

Chlordiazepoxide Overdosage: Manifestations of benzodiazepine overdosage include somnolence, confusion, coma and diminished reflexes. Dialysis is of limited value. There have been occasional reports of excitation in patients following benzodiazepine overdosage; if this occurs, barbiturates should not be used. Withdrawal symptoms of the barbiturate type have occurred after the discontinuation of benzodiazepines (see DRUG ABUSE AND DEPENDENCE section). Since Limbitrol contains amitriptyline, it is important to note that use of the benzodiazepine antagonist flumazenil is contraindicated in patients who are showing signs of serious cyclic antidepressant overdose.

DOSAGE AND ADMINISTRATION: Optimum dosage varies with the severity of the symptoms and the response of the individual patient. When a satisfactory response is obtained, dosage should be reduced to the smallest amount needed to maintain the remission. The larger portion of the total daily dose may be taken at bedtime. In some patients, a single dose at bedtime may be sufficient. In general, lower dosages are recommended for elderly patients.

Limbitrol DS (double strength) Tablets are recommended in an initial dosage of 3 or 4 tablets daily in divided doses; this may be increased to 6 tablets daily as required. Some patients respond to smaller doses and can be maintained on 2 tablets daily.

Limbitrol Tablets in an initial dosage of 3 or 4 tablets daily in divided doses may be satisfactory in patients who do not tolerate higher doses.

HOW SUPPLIED: *DS (double strength) Tablets,* containing 10 mg chlordiazepoxide and 25 mg amitriptyline (as the hydrochloride salt)--bottles of 100 and 500.

Tablets, containing 5 mg chlordiazepoxide and 12.5 mg amitriptyline (as the hydrochloride salt)--bottles of 100 and 500.

Roche Products

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